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REVIEW

COVID-19 Vaccines: Should We Fear ADE?

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Might COVID-19 vaccines sensitize humans to antibody-dependent enhanced (ADE) breakthrough infections? This is unlikely because coronavirus diseases in humans lack the clinical, epidemiological, biological, or pathological attributes of ADE disease exemplified by dengue viruses (DENV). In contrast to DENV, SARS and MERS CoVs predominantly infect respiratory epithelium, not macrophages. Severe disease centers on older persons with preexisting conditions and not infants or individuals with previous coronavirus infections. Live virus challenge of animals given SARS or MERS vaccines resulted in vaccine hypersensitivity reactions (VAH), similar to those in humans given inactivated measles or respiratory syncytial virus vaccines. Safe and effective COVID-19 vaccines must avoid VAH.

Keywords. dengue; dengue hemorrhagic fever; antibody-dependent enhancement (ADE); vaccine adverse events; coronavirus; SARS-CoV-2; immunopathology; vaccine; hypersensitivity; T cells.

Not since pandemic smallpox or the 1918 influenza have humans confronted an epidemic viral pathogen as successful as severe acute respiratory syndrome coronavirus 2 (SAR- CoV-2), a member of a family of viruses that cause serious diseases in many vertebrates [1]. It has proved difficult to achieve robust vaccine protection against avian, bovine, porcine, canine, and feline coronaviruses, failures sometimes attributed to antibody-dependent enhancement (ADE) [2]. The possibility that a SARS-CoV-2 vaccine may sensitize recipients to ADE has received considerable scrutiny [3]. On inspection, ADE is not 1 but 2 vaccine-related immunopathological phenomena: intrinsic ADE (iADE) and vaccine hypersensitivity (VAH). iADE describes interactions between microbial pathogen IgG antibody immune complexes that attach to Fc receptors to initiate infection but also enhance replication of the microbe by suppressing innate cellular defenses [4, 5]. VAH was first described in humans in the early 1960s, after formalin-inactivated measles vaccines were introduced in the United States and Europe. Within months, large numbers of vaccinated children developed a severe breakthrough disease, called atypical measles [6]. A similar outcome, vaccine-associated enhanced respiratory disease (VAERD), was observed in infants aged 4–12 months who were given formalin-inactivated respiratory syncytial virus (RSV) and a few months later infected by RSV [7]. The outcomes observed were attributed to delayed-type hypersensitivity and/or an Arthus reaction [8]. Lung lesions revealed damage to parenchymal tissue, a pulmonary neutrophilia with abundant macrophages and lymphocytes, and excess eosinophils. From studies in laboratory animals, it is thought that formalin-deconformed viral antigens raised nonprotective antibodies that led to a Th2 polarization of the immune response and a deficit of cytotoxic T cells. It was also the case that mice immunized with RSV inactivated with UV radiation, a purified fusion (F) protein, or a vaccinia-RSV replicative construct experienced similar pathology following challenge with wild-type virus. A similar pathological response has repeatedly accompanied live virus challenge in several species of laboratory animals vaccinated with SARS and Middle East respiratory syndrome (MERS) CoV constructs, with and without adjuvants [9, 10]. VAH may best be defined as a Coombs type III antigen hypersensitivity. It should be emphasized there is no formal proof that VAERD is antibody mediated. The mechanism(s) of the postmeasles vaccine disease enhancement and its similarity to VAERD are not known.

The biological behavior of some coronaviruses in nonhuman species, together with evidence that human coronavirus antibodies enhanced infection of SARS or MERS CoVs in Fc receptor-bearing cells in vitro, have led to speculations that ADE contributes to disease severity in humans [11]. It has been reported that high levels of SARS-CoV-1 IgG antibodies circulated in severe SARS cases and that anti-S IgG neutralizing antibody responses developed significantly faster after the onset of clinical symptoms in fatal compared with recovered cases, leading some to attribute enhanced tissue damage to ADE [12]. Because sera from SARS or MERS vaccinated animals' sera enhanced CoV infections in vitro, it was assumed that postvaccination pathologies, too, were ADE responses [13].

DENGUE ADE

If SARS or MERS infection outcomes are affected by iADE they should have epidemiological and disease features in common

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with dengue virus (DENV). These are compared in Table 1. In vivo, iADE requires an initial immunological event, termed sensitization. In dengue, this occurs in 3 settings: (1) first infections [26], (2) multitypic dengue antibodies passively transferred to infants (high antibody levels protect, low levels enhance) [27], and (3) vaccination resulting in incomplete protective immunity [14, 15]. Crucial to the occurrence of iADE is the circulation of 4 antigenically related DENVs. After a first infection, there is a 1 to 2-year period of relative cross-protection after which heterotypic DENV infection may cause severe disease [28]. Third or fourth sequential infections are not pathogenic. Preoutbreak age-specific distributions of dengue antibodies control age-specific ADE disease attack rates. During heterotypic infections, viremias may be enhanced early but as illness progresses the titers and duration of viremias are shortened [16].

Dengue disease is a serious and widespread global health problem. In many dengue-endemic countries there is an estimated 2% lifetime risk of hospitalization for enhanced dengue disease [29]. Severe DENV iADE infections are short-duration illnesses that elicit a stereotypical clinical course: an abrupt onset of fever and generalized symptoms followed around the time of defervescence by a rapid loss of fluid from the vascular compartment and, in turn, anoxia, shock, and gastrointestinal hemorrhage [30]. The first suggestion of an immunopathology was finding that DENV infected peripheral blood leukocytes (PBL) from dengue-immune monkeys and humans but not PBLs from nonimmune donors [31]. Severe DENV infections in infants implied that antibodies were etiological factors, a hypothesis confirmed when antibody-mediated enhanced DENV infection was produced in monkeys [32]. Peak viremia titers observed early in the illness are predictive of severe dengue in humans [16]. Careful pathological studies identified splenic and lymph node monocytes, macrophages, and dendritic cells as major targets of DENV infection [17]. Fluid loss from the vascular compartment is attributed to capillary damage caused by circulating toxic viral protein (nonstructural protein 1 [NS1]) [33]. In humans, disruption of endothelial glycocalyx components by NS1 correlates with plasma leakage during severe DENV infection [34]. DENV NS1-induced endothelial cell intrinsic pathway vascular leakage is related to loss of integrity of endothelial glycocalyx components both in vitro and in vivo and is independent of inflammatory cytokines [35].

Two corollary iADE phenomena have been described: (1) passively acquired dengue antibodies efficiently enhance infection/disease, and (2) disease severity rates may increase rapidly during epidemics. Severe dengue accompanies first infections in infants circulating dengue antibodies acquired from multi-immune mothers [36]. During the course of secondary DENV 2 epidemics in Cuba in 1981 and 1997, disease severity increased month to month. It has been suggested that a single amino acid mutation in NS1 may have increased disease severity by enhancing viremia or improving efficiency of transmission of virus by vector mosquitoes [37].

SARS ADE?

A coronavirus disease of cats, feline infectious peritonitis (FIP), causes classic ADE disease [38]. The dominant in vivo

Table 1. Dengue vs SARS-CoV-1 and SARS-CoV-2: Antibody-Dependent Enhancement Checklist

Risks	Dengue	SARS-CoV-1 and SARS-CoV-2
Sensitizing agent	4 dengue viruses	Unknown
Host cell infected	Predominantly monocytes, macrophages, mature dendritic cells [19]	Predominantly pulmonary epithelium [18]
Infected organs	Lymph nodes, spleen [17]	Lung, other organs
Sequence	2nd heterotypic DENV infection [20]	Unknown
Specific sequence	12 possible 2nd infection sequences, some more pathogenic than others [20]	Unknown
Immunity post 1st infection, homologous	Lifetime	Presumed long duration protection against homologous virus
Immunity post 1st infection, heterologous	1–2 y protection [21]	Unknown
Immunity post 1st infection, heterologous	Post 1–2 y, lifetime sensitization to ADE with 2nd infection [22]	Unknown
Immunity post 2nd infection	Lifetime protection	Unknown
Viremia	Peak enhancement early, duration 2nd infection shorter than 1st infection [16]	Unknown
Virus in tissues	RNA, viral antigen detected. No live virus [23]	Live virus isolated
Risk factors	Preexisting health conditions	Preexisting health conditions
Risk factors: age	Youngest and oldest at greatest risk	Oldest at greatest risk
Attack rates	Controlled by prevalence of 1st DENV infection antibodies [22].	No antibody effect observed
ADE with passive antibody	5 to 11-month-old infants born to DENV-immune mothers [22]	Not observed
Viral pathogenicity	Increases month to month, single mutation controls [24]	Not observed
Vaccine ADE	Dengvaxia raises nonprotective (ADE) antibodies, sensitizing nonimmunes [14, 15]	Challenge virus produces VAH in vaccinated animals [9, 10, 25]

Abbreviations: ADE, antibody-dependent enhancement; DENV, dengue virus; SARS-CoV, severe acute respiratory syndrome coronavirus; VAH, vaccine hypersensitivity reaction.

target for FIPV infection is peritoneal macrophages. Passively acquired maternal antibodies convert FIPV infections in kittens from a mild disease to one with fatal outcome. Many FIP vaccine constructs have sensitized animals to breakthrough ADE infections. In contrast to FIP, SARS and MERS CoV infections in humans predominantly affect the respiratory tract and other organs but not the reticuloendothelial system. A prevailing hypothesis is that SARS-CoV-1 and 2 enter cells via attachment of spike (S) protein to the ACE2 receptor. Most patients who die of SARS develop an acute respiratory distress syndrome [18]. Age-based case fatality ratios for SARS and coronavirus disease 2019 (COVID-19) are similar. During 2001–2003, among those infected with SARS-CoV-1, fatalities occurred in less than 1% of those under 25 years old, 6% among those aged 25–44 years, 15% in those aged 45–64 years, and more than 50% in those 65 years or older [18]. SARS-CoV-1 is a viral infection of alveolar epithelium resulting in diffuse alveolar damage, epithelial necrosis, and fibrin and hyaline deposition accompanied by an infiltration of multinucleated giant cells with evidence of infection of macrophages in the alveoli and in lung interstitium [39]. The principal target of infection is alveolar epithelial cells, apparently directly damaged by virus [39]. Severe diarrhea is not matched with corresponding intestinal pathology and there is a discrepancy between the histological damage and widespread viral infection of liver, distal convoluted renal tubules, sweat glands, parathyroid, pituitary, pancreas, adrenal gland, skeletal muscle, and cerebrum [40]. SARS-CoV-1 infections are of long duration, characterized by virus shedding from the intestines, respiratory secretions, and sweat exhibits an increase in infection intensity during the course of illness [40]. SARS-CoV-1 infections usually result in a normal IgM to IgG transition, although IgG antibodies were sometimes observed as early as 4 days after onset of illness. It is thought that competent T-cell immunity is essential for recovery [41].

While many clinical and pathological features are shared by SARS, MERS, and COVID-19, lungs from patients with COVID-19 show distinctive severe endothelial injury associated with the presence of intracellular virus and disrupted cell membranes. Histological analysis of pulmonary vessels in patients with COVID-19 showed widespread thrombosis, microangiopathy, and a reactive angiogenesis [42]. Indeed, there is growing evidence of thromboembolic phenomena in COVID-19 [43]. In severe and fatal SARS and MERS the dominance of the inflammatory response gave rise to the concept that cellular damage was due to a "cytokine storm" [44]. Because cytokines are stimulated by viral infection itself, it is difficult to distinguish between cytokines as cause or effect of infection. In dengue, capillary damage has been attributed to a cytokine storm. Instead, recent data suggests damage results from a circulating viral toxin [33].

CONCLUDING REMARKS

With others, we conclude that the differences in clinical, epidemiological, and pathological features of SARS and DENV diseases suggest that iADE does not contribute to the severity of natural human coronavirus infections [3]. Because myeloid cells are not major targets of infection, vaccine-derived nonprotective coronavirus antibodies are not expected to produce iADE infections in humans. High case fatality rates in elderly persons with preexisting conditions together with laboratory and autopsy studies support the contention that SARS-CoV-1 and 2 are direct pathogens, centering on type II pneumocytes, well-differentiated bronchial epithelial cells, and other parenchymal cells [45]. If SARS-CoV-1 or 2 infection severity were modified by enhancing antibodies acquired earlier in life, severe and fatal cases should cluster in age groups reflecting the time of that past infection. A past infection age cluster effect is illustrated by the 2001 severe DENV 1 outbreak in Tahitian children [46]. The island-wide DENV 1 and 3 infections that occurred in 1988–1990 protectively immunized older children. However, children born after 1990 were sensitized by DENV 2 infections during 1996–1997, explaining the occurrence of severe secondary DENV 1 disease in 4–12 year olds in 2001 [46].

A question asked frequently is whether SARS or MERS CoV infections convey solid protective immunity. Viral respiratory infections often fail to protect the respiratory tract from reinfection by the same organism. Among immune individuals, respiratory tract superinfections occur frequently but usually without systemic disease [47]. For example, natural and vaccine immunes were reinfected with measles or rubella viruses and these infections may contribute to the spread of virus [48].

VAH is a postvaccination outcome that may be associated with nonprotective antibodies. VAH is a complex and poorly defined immunopathology. Several different SARS and MERS vaccines have been shown to elicit a postchallenge VAH in laboratory animals. Ominously, when SARS-CoV-1–immune monkeys were challenged with homologous virus most animals had evidence of lung inflammation [47]. It is important to note that inactivated measles vaccine and Dengvaxia exhibited short-term protection [6, 14]. A central challenge to SARS-CoV-2 vaccine development will be differentiating early from sustained protection and will be greatly aided by a SARS-CoV-2 model of VAH in laboratory animal models. Recognition of vaccine constructs that achieve solid protection in humans might be accelerated by challenge of vaccinated human volunteers with live SARS-CoV-2 [49]. Better understanding of the clinical and immunological behavior of SARS-CoV-2 itself might be achieved through direct infections of human volunteers [50]. Given the magnitude of the repertoire of COVID-19 problems and the need for an effective vaccine, the full force of worldwide investigative resources should be directed at unraveling the pathogenesis of VAH.

Notes

Potential conflicts of interest. Both authors: No reported conflicts of interest. Both authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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